Prognostic role of intraparotid lymph node metastasis in primary parotid cancer : Systematic review

Guntinas-Lichius, Orlando

2021-03

Guntinas-Lichius , O , Thielker , J , Robbins , K T , Olsen , K D , Shaha , A R , Mäkitie , A A , de Bree , R , Vander Poorten , V , Quer , M , Rinaldo , A , Kowalski , L P , Rodrigo , J P , Hamoir , M & Ferlito , A 2021 , ' Prognostic role of intraparotid lymph node metastasis in primary parotid cancer : Systematic review ' , Head & Neck , vol. 43 , no. 3 , pp. 997-1008 . https://doi.org/10.1002/he

http://hdl.handle.net/10138/339660
https://doi.org/10.1002/hed.26541

Received: 1 August 2020 | Revised: 30 September 2020 | Accepted: 30 October 2020

DOI: 10.1002/hed.26541

CLINICAL REVIEW

WILEY

Prognostic role of intraparotid lymph node metastasis in primary parotid cancer: Systematic review

Orlando Guntinas-Lichius MD[1,2,3] | Jovanna Thielker MD[1,2] | K. Thomas Robbins MD, FRCSC, FACS[4] | Kerry D. Olsen MD[5] | Ashok R. Shaha MD[6] | Antti A. Mäkitie MD, PhD[7,8,9] | Remco de Bree MD, PhD[10] | Vincent Vander Poorten MD, PhD, MSc[3,11] | Miquel Quer MD, PhD[3,12] | Alessandra Rinaldo MD, FRCSEd ad hominem, FRCS (Eng, Ir) ad eundem, FRCSGlasg, FACS[13] | Luiz Paulo Kowalski MD, PhD[14] | Juan Pablo Rodrigo MD, PhD[15] | Marc Hamoir MD[16] | Alfio Ferlito MD, DLO, DPath, FRCSEd ad hominem, FRCS (Eng, Glasg, Ir) ad eundem, FDSRCS ad eundem, FACS, FHKCORL, FRCPath, FASCP, IFCAP[17]

[1]Department of Otorhinolaryngology, Jena University Hospital, Friedrich Schiller University, Jena, Germany

[2]Facial Nerve Center, Jena University Hospital, Friedrich Schiller University, Jena, Germany

[3]Multidisciplinary Salivary Gland Society, Geneva, Switzerland

[4]Department of Otolaryngology-Head and Neck Surgery, Southern Illinois University, Springfield, Illinois

[5]Department of Otorhinolaryngology, Mayo Clinic, Rochester, Minnesota

[6]Head and Neck Service, Memorial Sloan-Kettering Cancer Center, New York, New York

[7]Department of Otorhinolaryngology-Head and Neck Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[8]Research Program in Systems Oncology, Faculty of Medicine, University of Helsinki, Helsinki, Finland

[9]Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska Institute and Karolinska Hospital, Stockholm, Sweden

[10]Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

[11]Otorhinolaryngology-Head and Neck Surgery, University Hospitals Leuven and Department of Oncology, Section Head and Neck Oncology, Leuven, Belgium

[12]Department of Otolaryngology, Hospital Santa Creu i Sant Pau, Barcelona, Spain

[13]University of Udine School of Medicine, Udine, Italy

[14]Department of Head and Neck Surgery and Otorhinolaryngology, A.C. Camargo Cancer Center, and Division of Head and Neck Surgery, Sao Paulo State University Medical School, São Paulo, Brazil

[15]Servicio de Otorrinolaringología, Hospital Universitario Central de Asturias, Instituto Universitario de Oncología del Principado de Asturias, Universidad de Oviedo, Oviedo, Spain

[16]Department of Head & Neck Surgery, St Luc University Hospital and King Albert II Cancer Institute, Brussels, Belgium; Institut de Recherche Expérimentale et Clinique (IREC), Université Catholique de Louvain, Brussels, Belgium

[17]Coordinator of the International Head and Neck Scientific Group, Padua, Italy

This paper was written by members and invitees of the International Head and Neck Scientific Group (www.IHNSG.com)

Correspondence
Orlando Guntinas-Lichius, MD, Department of Otorhinolaryngology, Jena University Hospital, Am Klinikum 1, D-07747 Jena, Germany.
Email: orlando.guntinas@med.uni-jena.de

Section Editor: Eisele David

Abstract

Background: The prognostic importance of intraparotid lymph node metastasis (P+) in patients with primary parotid gland carcinoma is unclear.

Methods: Nineteen retrospective and noncomparative cohort studies, published between 1992 and 2020, met the inclusion criteria and included 2202 patients for this systematic review.

Results: The pooled prevalence of the P in adult patients in the unselected studies was 24.10% (95% confidence interval = 17.95-30.25). The number of P+ lymph nodes per patient was counted in only three studies and ranged from 1 to 11. The 5-year recurrence-free survival rate based on Kaplan-Meier analysis varied from 83% to 88% in P− patients compared to 36% to 54% in P+ patients. The average hazard ratio for tumor recurrence in patients with P+ compared to P− was 2.67 ± 0.58.

Conclusions: P+ is an independent negative prognostic factor in primary parotid gland cancer and should be included into the treatment planning.

KEYWORDS

clinical significance, intraparotid lymph node metastasis, nodal metastasis, prevalence, primary parotid cancer, survival

1 | INTRODUCTION

During embryology, the lymphatic system of the neck develops after encapsulation of the submandibular and sublingual glands but before encapsulation of the parotid glands. This is why the submandibular and sublingual glands do not contain intraglandular lymph nodes, whereas the parotid glands contain lymph nodes throughout the gland.[1,2] Cadaver dissections have shown that the number of lymph nodes in the superficial parotid lobe ranges from 0 to 22 and in the deep lobe from 0 to 4.[3-6] Some of the intraparotid lymph nodes (P) can also be identified by lymphatic mapping during a parotid sentinel node procedure.[7] For regional cutaneous squamous cell carcinoma and melanoma, it has been well known for a long time that metastasis to intraparotid lymph nodes (P+) is a negative prognostic factor compared to the absence of intraparotid lymph nodes (P−), all of which are independent of neck lymph node status.[8,9] However, these lymph nodes can also be associated with primary parotid cancer. In recent years, studies of parotid cancer[10-13] have reported the metastatic rate to intraparotid lymph nodes and concluded that P+ is an independent risk factor for poor outcomes for primary parotid cancer. The current UICC staging system for local lymph node metastasis (N) does not differentiate between the presence of cervical nodal disease vs parotid lymph node disease.[14] The protocols for managing patients with positive intraparotid lymph nodes are not well defined including the issue of staging and therapy. For example, should one positive intraparotid lymph node <3 cm in a case of a metastasis-free neck classified as N1? Should several positive intraparotid lymph nodes <6 cm in a metastasis-free neck be classified as N2b? Finally, there are no standards for pathologic analysis and reporting of a parotid gland specimen with a primary cancer. Therapeutic guidelines for P+ primary salivary gland cancer are needed.

This systematic study sought to review the current evidence for the role of P+ in primary parotid cancer. The main outcome measure was the prevalence of P+ and secondary outcomes were the number of positive intraglandular lymph nodes, the relationship of P+ to other oncological and histopathological parameters especially local recurrence and survival.

2 | MATERIALS AND METHODS

2.1 | Literature search strategy

This systematic review followed The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] An online literature search was

performed using the PubMed, SCOPUS, Embase, Web of Science, Google Scholar, and Cochrane Central Register of Controlled Trials databases from the date of first publication in these databases to June 30, 2020. The search strategy aimed to capture all papers on intraparotid lymph nodes involvement and metastases in parotid cancer. The search terms were "primary parotid cancer," "primary parotid carcinoma," "parotid neoplasm," "intraparotid lymph node," "parotid lymph nodes," "intraglandular," "lymphatic metastasis," and "lymph nodes." Two authors (OGL, JT) independently reviewed the reference lists, the titles, and abstracts for potentially eligible studies. Both review authors independently assessed each full-text paper for eligibility and then selected the studies for inclusion. There were no disagreements about inclusion.

2.2 | Selection criteria

Studies were selected based on the ideas behind the PICO model.[16] The C (comparison) of the PICO concept was excluded since comparison studies are not existing on the topic and were therefore not the focus for this systematic review. Studies had to meet the following inclusion criteria: (a) English language; (b) primary presentation of cancer to the parotid gland; (c) primary parotid cancer; (d) no prior treatment of the parotid gland or neck for malignancy; (e) detailed surgical description of the affected parotid gland and its outcomes; and (f) mean follow-up of >24 months. Exclusion criteria included (a) studies with non-primary tumors; (b) no surgical treatment of the affected parotid gland; (c) prior treatment of the affected parotid gland or prior treatment of the neck; (d) cohort studies with less than 20 patients; and (e) case reports.

2.3 | Quality assessment

Two authors (OGL, JT) independently evaluated the methodological quality of the included studies. For evaluation, the criteria from the "guidelines for assessing the quality in prognostic studies on the basis of Framework of Potential Biases" was used.[17,18] These quality criteria included six domains of potential bias with prognostic studies: study population, study attrition, measurement of prognostic factors, measurement of outcomes, measurement of and controlling for confounding variables, and analysis approaches. The reviewers graded each criterion as yes = 2, partly = 1, or no/unclear = 0. In case of disagreement between the two reviewers, the study was discussed until a consensus was found. A quality score for each study was calculated as the sum of all scores, thus ranging between 0 and 12 points where higher scores indicated better quality. No weighting was used.

2.4 | Outcome measurements and statistics

For the primary outcome, we calculated the prevalence of intraparotid metastasis. Secondary outcome measures were the number of intraparotid lymph node metastases; the association between P+ and other tumor-related parameters (T and N classification, perineural invasion, positive margins, lymphovascular invasion, tumor grade); and finally the impact of P+ on recurrence-free survival and overall survival. All descriptive statistical analyses were performed using the IBM SPSS program, version 25. Data from each study on the P+ rate were extracted and recorded in an Excel (Microsoft) spreadsheet. The pooled prevalence of P+ with 95% confidence interval (CI) was calculated. The results are presented with a forest plot. Statistical heterogeneity was calculated with the Higgins I^2 statistics[19] Other data (number of P+, follow-up time, survival rates, hazard ratios) are expressed as mean ± SD and ranges.

3 | RESULTS

The search identified 139 articles. Duplicates were removed. From the remaining 100 abstracts, 80 publications were excluded Table S1). The full texts of the remaining 20 articles were reviewed. Nineteen studies were included (Figure 1).[11-13,20-35] There were no

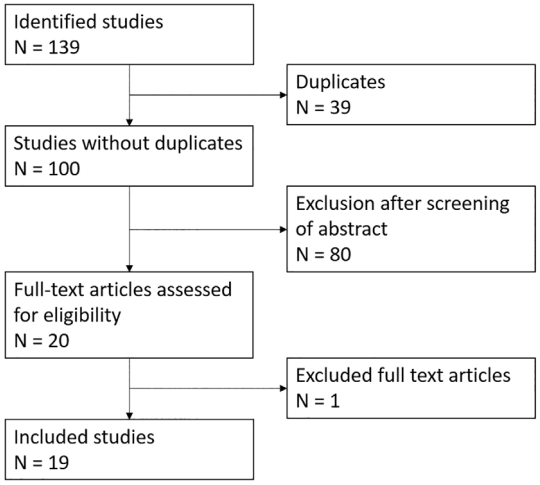

FIGURE 1 Literature search flow chart according to the PRISMA guidelines[15]

TABLE 1 Characteristics and findings of the included studies

Study	Year	n	Population	Subtypes of parotid cancer	Follow up time (months)	P + %	P+ (n)	P+ association	Outcome RFS rate %	Outcome OS rate %	Outcome RFS P+	Outcome OS P+
Armstrong et al [20]	1992	30	1939-1982	All, 90 with ND; focus on cN0	—	53.3 in cN0	—	—	—	—	—	—
Cheng et al [21]	2019	249	2002-2015	All, focus on neutrophil-to-lymphocyte ratio	Mean 89.4 (range, 8-190)	18.1	—	—	—	—	—	HR 1.845 (1.054-4.531) $P = .003$
Fang et al [22]	2019	53	2005-2016	SCC	Mean 67.3 (range, 4-135)	43.3	—	—	—	—	HR 2.347 (CI 1.279-5.612) $P = .007$	Not significant
Fang et al [23]	2019	144	2000-2014	AcCC focus on rM +	Mean 90.7 (range, 16-211)	31.8	—	—	—	—	—	Distant metastasis survival P+ (1.854 [1.061-4.144], $P = 0.011$
Fang et al [24]	2019	73	1990-2017	Pediatric MEC	Mean 95.4 (range, 13-286)	17.8					HR 2.223 (CI 1.658-5.897) $P < .001$	HR 1.897 [1.142-4.656]) $P < .001$
Feng et al [13]	2019	337	2000-2017	All	Mean 71.7 (range, 4-209)	32.9	Mean 1.4 (range, 1-5).	Higher T classification, higher pN classification, perineural invasion, R+, lymphovascular invasion	All 96 5y all 94 10y P+ ≤2 LN 65 5y 56 10y P+ >2 LN 22 5y 22 10y	—	P+ ≤ 2 LN RR 6.175 CI 2.797-13.634) $P < .001$ P+ > 2 LN RR 21.563 (CI 7.450-62.415) $P < .001$	—
Grasl et al [25]	2019	66	1998-2017; 1989-2005	AcCC	Mean 55.5 (median 46.7)	7.6	—	No influence on recurrence, no influence on grading	—	—	—	—
Klussmann et al [11]	2008	142	1986-2006	All	Median 24.4 (range, 0.2-250.5).	17.6	Range 0-11	—	P+ not significant	P+ not significant	—	—
Lim et al [12]	2014	86	1998-2009	All	Median 42 cN0 median 36 cN+ median 38 P− median 34 P+	38.7		N classification	—	P− 75 3y P+ 34.2 3y $P = 0.0037$	—	—

TABLE 1 (Continued)

Study	Year	n	Population	Subtypes of parotid cancer	Follow up time (months)	P + %	P+ (n)	P+ association	Outcome RFS rate %	Outcome OS rate %	Outcome RFS P+	Outcome OS P+
Lima et al [26]	2005	126	1974-1998	All	Mean 60 (range, 4-216)	12.0	—	—	—	—	—	—
Nisa et al [27]	2015	95	1997-2010	All	Median 38.41 (range, 0.46-160.75)	25.26	Median 1; mean 2.91; range, 1–10).	Higher pT, higher pN, higher overall stage; high-risk carcinomas, treatment failures	P+ 36 5y P- 85 5y	P+ 70 5y P- 78 5y	—	—
Niu et al [28]	2019	190	2001-2017	MEC	Mean 71.1	24.7	—	Higher T classification, higher N classification, perineural invasion, high grade, lymphovascular invasion	P- 88 10y P+ 54 10y $P < .001$.	—	HR 2.357 (CI 1.163-4.776) $P = .017$	—
Paderno et al[29]	2018	104	1997-2017	All	Median 51	20.2	—	Perineural invasion, higher grade, lateral lymph node involvement, extranodal extension	66.9 5y	74.7 5y	RR 3.64; $P = .00102$	RR 2.97; $P = .00881$
Schneider et al [30]	2020	50	1993-2010	All	Mean 98.2 (range, 4-275)	38.8	—	—	P+ 50 5y P– 80 5y	P+ not significant	—	—
Seng et al [31]	2020	77	2000–2017	Pediatric	Mean 85.0 (range, 13-173)	19.5	—	Higher tumor stage, high-grade tumor,	All 91 10y P+ 36 5y P– 97 5y	—	HR 2.805 (CI 1.697-5.119) $P < .004$	—
Shang et al [32]	2019	122	2000-2016	High-grade MEC	Mean 69.7 (range, 5-201)	48.4	—	Higher T classification, higher N classification	P– 83 5y P+ only superficial lobe parotid 56 5y P+ only deep lobe parotid metastasis, 24 5y P+ superficial and deep lymph node parotid 11 5y $P < .001$		P+ superficial lobe parotid HR 2.142 (CI 0.952-4.819) $P = .065$ P+ deep lobe parotid HR 5.659 (CI 1.958-16.355) $P = .001$ P+ superficial and deep parotid lobe HR 13.517 (CI 4.934-37.033) $P < .001$	
Stenner et al [33]	2012	70	1987-2009	All, T1-2	Median 51.7 (range, 0.2-191.5)	73.3	—	—	—	—	—	—
Stodulski et al [34]	2017	66	1992-2010	All, focus on cN0	Mean 94.8 (range, 60-288)	13.6	—	Occult N+	—	—	—	—

(Continues)

TABLE 1 (Continued)

Study	Year	n	Population	Subtypes of parotid cancer	Follow up time (months)	P + %	P+ (n)	P+ association	Outcome RFS rate %	Outcome OS rate %	Outcome RFS P+	Outcome OS P+
Wu et al[35]	2020	122	2005-2018	MEC	Mean 77 (range, 6-147)	24.6	—	Higher T classification, higher N classification, perineural invasion, high grade, lymphovascular invasion	—	—	P1 HR 1.338 (CI 0.913-2.116) $P = .063$ P2 HR 1.992 (CI 1.039-3.668) $P = 0.011$ P3 HR 3.118 (CI 1.229-7.194) $P = .001$	—

Abbreviations: 5y, 5 year; 10y, 10 year; AcCC, acinic cell carcinoma; CI = 95% confidence interval; HR, hazard ratio; LN, lymph node; MEC, mucoepidermoid carcinoma; ND, neck dissection; OS, overall survival; P+, intraparotid lymph node metastasis; P−, no intraparotid lymph node metastasis; RFS, recurrence-free survival; RR, relative risk; SCC, squamous cell carcinoma.

prospective studies identified. Instead, all studies were retrospective and noncomparative trials. The 19 studies included a total of 2202 patients (Table 1).

3.1 | Quality scores

For the 19 selected studies, the quality scores ranged from 6 to 9 points (Table S2). Twelve studies were classified medium quality (5-8 points) and seven studies as high quality (9-12 points). It is important to note that nine of the studies came from the same institution, the Zhengzhou University, China, with varying time periods, inclusion criteria, and the outcome measures.[13,21-24,28,31,32,35] All but one study were single institutional noncomparative cohort studies. One study collected data from two centers.[25] Twelve studies included all histological types of primary parotid cancer,[11-13,20,21,26,27,29-31,33,34] four studies were focused on mucoepidermoid cancer,[24,28,32,35] two studies on acinic cell carcinoma, [23,25] and one study on squamous cell carcinoma.[22] Two studies reported only pediatric cases[24,31] and one study focused only on early-stage (low-volume) cancer (T1/T2 N0M0).[33] Because parotid cancer is relatively rare, long inclusion periods were chosen in all studies. Important limitations were the variability of the extent of the parotidectomy, unclear evaluation of the intraparotid lymph nodes, limited, or inconsistent follow-up periods, and small subgroups limiting the explanatory power and the multivariate analyses.

3.2 | Primary outcome: Prevalence of P+

The mean relative number of P+, that is, the relation of positive nodes to all evaluated intraparotid lymph nodes was 29.55 ± 16.53% (range, 7.6%-73.3%). The pooled prevalence of the P+ rate in adult patients in the unselected studies was 24.10% (CI = 17.95-30.25; Figure 2). The pooled prevalence of the P+ rate in adult patients in different subtypes of parotid cancer was more variable with 29.00% (CI = 17.59-40.42; Figure 3). Only three studies stated the absolute number of nodes for each P+ case. [11,13,28] Herein, the number of P+ in each cohort ranged from 1 to 11. P+ was detected in both the superficial lobe and the deep lobe.

3.3 | Association of P+ with other tumor characteristics

Associations with other tumor characteristics were analyzed with univariate analyses in 10 studies (cf. Table 1).

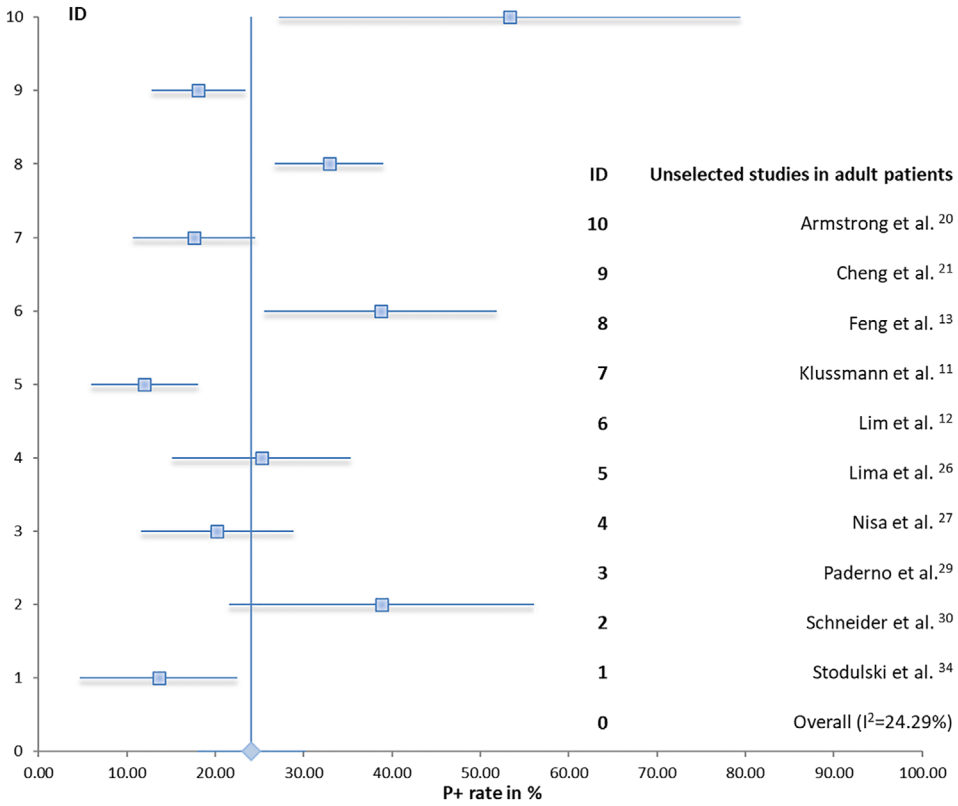

FIGURE 2 Forest plot of pooled prevalence of P+ in unselected studies on adult patients with primary parotid cancer. Weights are from random effect analysis. C, confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

In selected studies, P+ was more common with a higher T classification, higher pN classification, finding of perineural invasion, positive margins, lymphovascular invasion, and high-grade tumors. P+ had a higher risk of occult lymph node metastasis in the neck (N+) in one study.[34]

3.4 | Impact of P+ on recurrence-free survival and overall survival

The follow-up time of individual patients varied from 0.2 to 288 months. Only six studies reported median follow-up time data.[11,12,25,27,29,33] The average reported that median follow-up was 39.1 ± 9.9 months (range, 24.4-51.7). The remaining 13 studies provided the mean values of follow-up time: 78.9 ± 14.2 months (range, 55.5-98.2). Nine studies reported data on recurrence-free survival.[13,22,24,27-29,31,32,35] Nine studies provided data on overall survival.[11,12,21-24,27,29,30] P+ was a significant negative prognostic factor for survival in all the multivariate regression models except one. The 5-year recurrence-free survival rate in Kaplan-Meier analysis varied from 83% to 88% (97% in children) in P− patients compared to 36% to 54% in P+ patients. If >2 lymph nodes were positive and if lymph nodes in the deep lobe were involved, the 5-year recurrence-free survival rate dropped to 11% to 22%. The average calculated hazard ratio for tumor recurrence in patients with P+ compared to P− was 2.67 ± 0.58 (range, 2.22-3.64). Only one study presented 5-year overall survival rates. Here, patients with P+ had a 5-year survival rate of 70% compared to 78% in P− patients. The average calculated hazard ratio for a risk of death in patients with P+ compared to P− was increased by 2.14 ± 0.55 (range, 1.85-2.97) in four studies.[21,23,24,29] However, one study did not show a significant difference in the risk for death between P+ and P− patients in the Cox regression analysis.[22]

4 | DISCUSSION

The parotid gland has between 0 and 26 intraparotid lymph nodes.[3,6] Many patients did not have P+ metastasis. Hence, intraparotid lymph node metastasis does not seem to be first echelon lymph nodes for regional spreading in all cases. It may be that the location of the primary tumor in the parotid gland influences if an intraparotid lymph node metastasis can take place or not because the lymphatics flow from superior to inferior portion of the gland. It is imaginable that if the tumor is located in the far inferior part of parotid gland, level IIa or IIb lymph node metastasis might regularly occur without intraparotid lymph node metastasis. The presented data are too sparse allowing a detailed analysis of the intraparotid lymphatic metastasis routes. Furthermore,

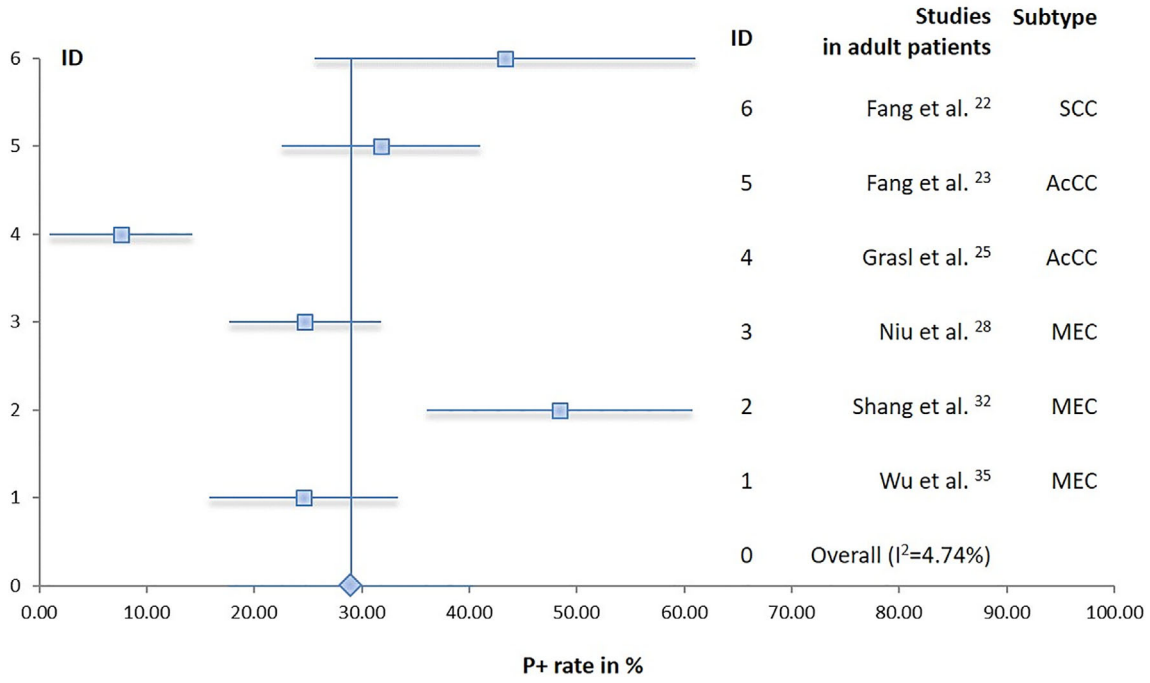

FIGURE 3 Forest plot of pooled prevalence of P+ in studies in adult patients focused on a histological subtype of primary parotid cancer. Weights are from random effect analysis. AcCC, acinic cell carcinoma; CI, confidence interval; MEC, mucoepidermoid carcinoma; SCC, squamous cell carcinoma [Color figure can be viewed at wileyonlinelibrary.com]

only a few of the presented studies undertook the effort to distinguish between metastasis in the superficial and the deep lobe of the parotid gland. It can only be stated that in some patients with P+ in the superficial gland, regional metastasis to the upper neck cervical lymph nodes occurred without P+ in the deep lobe, that is, bypassing the deep parotid gland. There is some limited evidence that P+ in the deep lobe has a worse prognostic than P+ in the superficial lobe.

Prospective studies using serial section histology to detect all possible intraparotid lymph nodes and the true finding of P+ in primary parotid cancer are lacking. Of the retrospective studies analyzed for the present systematic review, only three of the studies provided an absolute number positive lymph nodes among the patients with P+ disease.[11,13,28] All included studies reported the proportion of positive lymph nodes among P+ patients, which ranged from 7.6% to 73.3% with a pooled prevalence for the unselected studies in adult patients of 24.10% (CI = 17.95-30.25). Taking into account the methodological limitations of the included studies, it can be postulated that up to a third of all intraparotid lymph nodes in patients with primary parotid cancer may be positive for metastatic cancer. Most studies showed that the presence of P+ was an independent predictor for lower recurrence-free survival.[13,22,24,28,29,31,32,35] Patients with P+ had a 2- to 3-fold higher risk for tumor recurrence than patient with P−. The relationship of P+ to overall survival was analyzed in only four studies.[21,23,24,29] In these reports, P+ had a 2-fold higher risk of death compared to P−. Overall, the data on the 2202 patients included into this review suggest that P+ is an important independent predictor of a worse outcome in patients with primary parotid cancer.

The significance of intraparotid lymph node metastasis has previously been examined for cutaneous squamous cell cancer (CSCC). O'Brien et al showed that P+ is an independent predictor for a worse outcome in CSCC, independent of the neck status.[8] This study led to the proposal of a revised staging system dividing the regional lymph node staging system into parotid and cervical disease, defined as "P" and "N" classifications (Table 2). Also the group at the Mayo clinics reported on the importance of this concept.[9] The attempt to demonstrate the independent outcome influence of intraparotid vs neck lymph nodes has so far not been incorporated into the AJCC nodal staging of metastatic CSCC.[36,37] Also for primary parotid cancer, the argument has been made to consider the intraparotid lymph nodes as an important entity.[10,38] The results of the present meta-analysis suggest denoting the intraparotid and neck lymph node metastases separately for improved staging of primary parotid cancer (Table 2). Wu et al classified 122 patients with parotid mucoepidermoid cancer (P0: n = 92, P1:

n = 10, P2: n = 16; P3: n = 4; definition of P classification, see Table 2).[35] Although the sample size was limited, they showed that the P classification of the intraparotid nodes was an independent prognostic factor for recurrence, independent from the N classification.

This systematic review has several limitations. All included trials were retrospective noncomparative cohort studies. The data did not allow a formal meta-analysis. Therefore, selection bias cannot be ruled out. The extent of the parotidectomy procedures and the histopathological analysis of the intraparotid lymph nodes were not standardized or the details were not presented in these studies. Nine of the 19 included studies came from the same institution in China,[13,21-24,28,31,32,35] and several of these studies focused more narrowly on specific histologic cancers.[22-25,28,32,35] This makes it likely that there was an overlap of patients among these nine studies.

Future studies should focus on histopathology standards defining the assessment of intraglandular lymph nodes in histopathology reports. The parotid surgeon should ask their pathologist to routinely look for intraparotid lymph nodes in all the parotid specimen.[39] Consensus papers for histopathology reporting of parotid gland neoplasms typically point out the importance of the lymph node metastasis but do not give any guidance on how to classify positive intraparotid lymph nodes in the current TNM staging system.[40] Most guidelines recommend at least a total parotidectomy at least for high-grade parotid cancer.[41,42] Total parotidectomy is the only way to assess the deep parotid nodes.[42]

In a recent systematic review based on nine retrospective studies (as no prospective trials were available), the question of performing a partial parotidectomy for a presumably benign tumor that proves to be a T1 low-grade

TABLE 2 Proposal for an improved staging of nodal metastasis of primary parotid cancer based on the American Joint Committee on Cancer,[14] the O'Brien revised staging system,[8] and the proposal made for metastatic cutaneous squamous cell cancer[37]

AJCC 8th edition	Proposed revised staging system	
N classification	**P classification**	**N classification**
NX = regional lymph nodes cannot be assessed	PX = parotid lymph nodes cannot be assessed	NX = regional lymph nodes cannot be assessed
N0 = no regional lymph node metastases	P0 = no intraparotid metastases	N0 = no regional lymph node metastases
N1 = metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)	P1 = metastatic node up to 3 cm in diameter in the parotid gland	N1 = metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2a = metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)	P2 = metastatic node more than 3 cm up to 6 cm diameter or multiple parotid nodes	N2a = metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b = metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)	P3 = metastatic node more than 6 cm in diameter or disease involving the facial nerve or skull base	N2b = metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c = metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)		N2c = metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3a = metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)		N3a = metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b = metastasis in a lymph node more than 3 cm in greatest dimension with extranodal extension (ENE+) or multiple ipsilateral, or any contralateral, or bilateral node(s) with extranodal extension (ENE+)		N3b = metastasis in a lymph node more than 3 cm in greatest dimension with extranodal extension (ENE+) or multiple ipsilateral, or any contralateral, or bilateral node(s) with extranodal extension (ENE+)

Abbreviations: AJCC, American Joint Committee on Cancer; ENE, extranodal extension.

malignancy with free margins in the final histopathology was raised based on the indication for removing all lymph nodes at risk.[43] Following the results of the present study, such limited approaches for parotid cancer have to be applied with caution. Much confusion would be eliminated, and guidelines as to when to remove all parotid tissue would be clearer, if all parotid specimens had a complete evaluation of their nodal status. Any finding of a positive node could be an indication for completing a total parotidectomy and neck dissection.

The studies analyzed for the present systematic review do not allow to draw the clear conclusion that smaller tumors have a lower risk for P+. If limited surgery less than a total parotidectomy is performed, an inclusion of the tumor bed and the nonresected parotid parts into the postoperative radiotherapy concept has to be discussed if postoperative radiotherapy is indicated for other reasons, or at least a close follow-up of the patient is recommended. In such a situation, radiotherapy might also be an alternative to avoid a second surgery with increased risk of facial nerve damage. In the absence of prospective studies, the question of whether radiotherapy or surgical therapy of intraparotid lymph node metastases has therapeutic efficacy for the patient remains completely unclear.[44] However, considering the higher risk of recurrence and poor salvage of recurrence with positive intraparotid lymph nodes, strong consideration should be given for postoperative radiation therapy. Whether the entire neck should be included in postoperative radiation therapy if the neck does not show any obvious disease either on imaging or after a neck dissection remains unclear. This dilemma mirrors the controversy of elective neck dissection (END) for cN0 parotid carcinoma, where several papers claim that elective neck irradiation is as effective as END.[45]

5 | CONCLUSION

The average finding of P+ ranged from 7.6% to 73.3% in this systematic review of parotid cancers, supporting the importance and need to evaluate and effectively treat the intraparotid lymph nodes. This implies a more rigorous pathology examination with a meticulous search for intraparotid lymph nodes in parotid cancer specimens. Prospective studies are needed to further define patients at risk for P+. Such patients may benefit from a total parotidectomy and should not undergo only a more limited parotid approach. Further study in this area should also focus on the value of (adjuvant) radiotherapy for positive intraparotid lymph nodes. Subsequent updates of the TNM staging for salivary gland cancer should consider the possible benefit of including the presence of intraparotid lymph node metastases in its associated classification of lymph node disease.

ACKNOWLEDGMENT

Open access funding enabled and organized by Projekt DEAL.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. All relevant data is presented in the manuscript.

ORCID

Orlando Guntinas-Lichius https://orcid.org/0000-0001-9671-0784
K. Thomas Robbins https://orcid.org/0000-0002-3255-8960
Ashok R. Shaha https://orcid.org/0000-0001-7478-9436
Remco de Bree https://orcid.org/0000-0001-7128-5814
Vincent Vander Poorten https://orcid.org/0000-0003-1341-829X
Luiz Paulo Kowalski https://orcid.org/0000-0002-0481-156X
Juan Pablo Rodrigo https://orcid.org/0000-0003-3063-0890
Marc Hamoir https://orcid.org/0000-0001-8547-2768
Alfio Ferlito https://orcid.org/0000-0002-8247-8002

REFERENCES

1. Holsinger FC, Bui DT. Anatomy, function, and evaluation of the salivary glands. In: Myers EN, Ferris RL, eds. *Salivary Gland Disorders*. Heidelberg: Springer; 2007.
2. Som PM, Miletich I. The embryology of the salivary glands: an update. *Neurographics*. 2015;5(4):167-177.
3. McKean ME, Lee K, McGregor IA. The distribution of lymph nodes in and around the parotid gland: an anatomical study. *Br J Plast Surg*. 1985;38(1):1-5.
4. Garatea-Crelgo J, Gay-Escoda C, Bermejo B, Buenechea-Imaz R. Morphological study of the parotid lymph nodes. *J Craniomaxillofac Surg*. 1993;21(5):207-209.
5. Pisani P, Ramponi A, Pia F. The deep parotid lymph nodes: an anatomical and oncological study. *J Laryngol Otol*. 1996;110(2):148-150.
6. Sonmez Ergun S, Gayretli O, Buyukpinarbasili N, et al. Determining the number of intraparotid lymph nodes: postmortem examination. *J Craniomaxillofac Surg*. 2014;42(5):657-660.
7. Ollila DW, Foshag LJ, Essner R, Stern SL, Morton DL. Parotid region lymphatic mapping and sentinel lymphadenectomy for cutaneous melanoma. *Ann Surg Oncol*. 1999;6(2):150-154.
8. O'Brien CJ, McNeil EB, McMahon JD, Pathak I, Lauer CS, Jackson MA. Significance of clinical stage, extent of surgery, and pathologic findings in metastatic cutaneous squamous carcinoma of the parotid gland. *Head Neck*. 2002;24(5):417-422.
9. Thom JJ, Moore EJ, Price DL, Kasperbauer JL, Starkman SJ, Olsen KD. The role of total parotidectomy for metastatic

cutaneous squamous cell carcinoma and malignant melanoma. *JAMA Otolaryngol Head Neck Surg*. 2014;140(6):548-554.
10. Boahene DK, Olsen KD, Lewis JE, Pinheiro AD, Pankratz VS, Bagniewski SM. Mucoepidermoid carcinoma of the parotid gland: the Mayo clinic experience. *Arch Otolaryngol Head Neck Surg*. 2004;130(7):849-856.
11. Klussmann JP, Ponert T, Mueller RP, Dienes HP, Guntinas-Lichius O. Patterns of lymph node spread and its influence on outcome in resectable parotid cancer. *Eur J Surg Oncol*. 2008;34 (8):932-937.
12. Lim CM, Gilbert MR, Johnson JT, Kim S. Clinical significance of intraparotid lymph node metastasis in primary parotid cancer. *Head Neck*. 2014;36(11):1634-1637.
13. Feng Y, Liu F, Cheng G, Fang Q, Niu X, He W. Significance of intraparotid node metastasis in predicting local control in primary parotid cancer. *Laryngoscope*. 2019;129(10):2309-2312.
14. Amin MB, Edge S, Greene F, et al. *AJCC Cancer Staging Manual*. 8th ed. Heidelberg: Springer; 2017.
15. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269. W264.
16. Cooke A, Smith D, Booth A. Beyond PICO: the SPIDER tool for qualitative evidence synthesis. *Qual Health Res*. 2012;22 (10):1435-1443.
17. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med*. 2006; 144(6):427-437.
18. Rashid M, Kristofferzon ML, Nilsson A, Heiden M. Factors associated with return to work among people on work absence due to long-term neck or back pain: a narrative systematic review. *BMJ Open*. 2017;7(6):e014939.
19. Neyeloff JL, Fuchs SC, Moreira LB. Meta-analyses and Forest plots using a microsoft excel spreadsheet: step-by-step guide focusing on descriptive data analysis. *BMC Res Notes*. 2012; 5:52.
20. Armstrong JG, Harrison LB, Thaler HT, et al. The indications for elective treatment of the neck in cancer of the major salivary glands. *Cancer*. 1992;69(3):615-619.
21. Cheng G, Liu F, Niu X, Fang Q. Role of the pretreatment neutrophil-tolymphocyte ratio in the survival of primary parotid cancer patients. *Cancer Manag Res*. 2019;11:2281-2286.
22. Fang Q, Wu J, Liu F. Oncologic outcome and potential prognostic factors in primary squamous cell carcinoma of the parotid gland. *BMC Cancer*. 2019;19(1):752. https://doi.org/10.1186/s12885-019-5969-6.
23. Fang Q, Wu J, Du W, Zhang X. Predictors of distant metastasis in parotid acinic cell carcinoma. *BMC Cancer*. 2019;19(1):475. https://doi.org/10.1186/s12885-019-5711-4.
24. Fang Q, Liu F, Seng D. Oncologic outcome of parotid mucoepidermoid carcinoma in pediatric patients. *Cancer Manag Res*. 2019;11:1081-1085.
25. Grasl S, Janik S, Grasl MC, et al. Nodal metastases in acinic cell carcinoma of the parotid gland. *J Clin Med*. 2019;8(9):1315. https://doi.org/10.3390/jcm8091315.
26. Lima RA, Tavares MR, Dias FL, et al. Clinical prognostic factors in malignant parotid gland tumors. *Otolaryngol Head Neck Surg*. 2005;133(5):702-708.
27. Nisa L, Salmina C, Dettmer MS, et al. Implications of intraglandular lymph node metastases in primary carcinomas of the parotid gland. *Laryngoscope*. 2015;125(9):2099-2106.
28. Niu X, Fang Q, Liu F. Role of intraparotid node metastasis in mucoepidermoid carcinoma of the parotid gland. *BMC Cancer*. 2019;19(1):417.
29. Paderno A, Tomasoni M, Mattavelli D, Battocchio S, Lombardi D, Nicolai P. Primary parotid carcinoma: analysis of risk factors and validation of a prognostic index. *Eur Arch Otorhinolaryngol*. 2018;275(11):2829-2841.
30. Schneider S, Kotowski U, Kadletz L, et al. Intraparotid and cervical lymph nodes metastasis in primary parotid gland carcinoma-impact on clinical outcome. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2020;129(6):570-574.
31. Seng D, Fang Q, Liu F, Luo R, Liu S. Intraparotid lymph node metastasis decreases survival in pediatric patients with parotid cancer. *J Oral Maxillofac Surg*. 2020;78(5):852 e851-852 e856.
32. Shang X, Fang Q, Liu F, Wu J, Luo R, Qi J. Deep parotid lymph node metastasis is associated with recurrence in high-grade mucoepidermoid carcinoma of the parotid gland. *J Oral Maxillofac Surg*. 2019;77(7):1505-1509.
33. Stenner M, Molls C, Luers JC, Beutner D, Klussmann JP, Huettenbrink KB. Occurrence of lymph node metastasis in early-stage parotid gland cancer. *Eur Arch Otorhinolaryngol*. 2012;269(2):643-648.
34. Stodulski D, Mikaszewski B, Majewska H, Wisniewski P, Stankiewicz C. Probability and pattern of occult cervical lymph node metastases in primary parotid carcinoma. *Eur Arch Otorhinolaryngol*. 2017;274(3):1659-1664.
35. Wu J, Fang Q, Liu F, Zhang X. Intraparotid node metastases in adults with parotid mucoepidermoid cancer: an indicator of prognosis? *Br J Oral Maxillofac Surg*. 2020;58(5):525-529.
36. Ch'ng S, Maitra A, Allison RS, et al. Parotid and cervical nodal status predict prognosis for patients with head and neck metastatic cutaneous squamous cell carcinoma. *J Surg Oncol*. 2008; 98(2):101-105.
37. Rotman A, Kerr SJ, Giddings CEB. Elective neck dissection in metastatic cutaneous squamous cell carcinoma to the parotid gland: a systematic review and meta-analysis. *Head Neck*. 2019; 41(4):1131-1139.
38. Olsen KD, Moore EJ. Deep lobe parotidectomy: clinical rationale in the management of primary and metastatic cancer. *Eur Arch Otorhinolaryngol*. 2014;271(5):1181-1185.
39. Thielker J, Grosheva M, Ihrler S, Wittig A, Guntinas-Lichius O. Contemporary management of benign and malignant parotid tumors. *Front Surg*. 2018;5:39.
40. Seethala RR, Altemani A, Ferris RL, et al. Data set for the reporting of carcinomas of the major salivary glands: explanations and recommendations of the guidelines from the international collaboration on cancer reporting. *Arch Pathol Lab Med*. 2019;143(5):578-586.
41. Sood S, McGurk M, Vaz F. Management of salivary gland tumours: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol*. 2016;130(S2):S142-S149.
42. Olsen KD, Quer M, de Bree R, Vander Poorten V, Rinaldo A, Ferlito A. Deep lobe parotidectomy-why, when, and how? *Eur Arch Otorhinolaryngol*. 2017;274(12):4073-4078.

43. Quer M, Olsen KD, Silver CE, et al. Is there a role for limited parotid resections for primary malignant parotid tumors? *Surgeries*. 2020;1:2-9.
44. Vander Poorten V, Bradley PJ, Takes RP, Rinaldo A, Woolgar JA, Ferlito A. Diagnosis and management of parotid carcinoma with a special focus on recent advances in molecular biology. *Head Neck*. 2012;34(3):429-440.
45. Valstar MH, van den Brekel MW, Smeele LE. Interpretation of treatment outcome in the clinically node-negative neck in primary parotid carcinoma: a systematic review of the literature. *Head Neck*. 2010;32(10):1402-1411.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Guntinas-Lichius O, Thielker J, Robbins KT, et al. Prognostic role of intraparotid lymph node metastasis in primary parotid cancer: Systematic review. *Head & Neck*. 2020;1–12. https://doi.org/10.1002/hed.26541